Annex XV dossier

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS SVHC(CMR)

Substance Name: **Diisobutyl phthalate**

EC Number: **201-553-2**

CAS Number: **84-69-5**

- *It is proposed to identify the substance as a SVHC according to Article 57(c).*

Submitted by Germany

Version: August 2009

CONTENTS

TABLES

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS SVHC (CMR)

Substance Name: **Diisobutyl phthalate**

EC Number: **201-553-2**

CAS number: **84-69-5**

- *It is proposed to identify the substance as a SVHC according to Article 57 (c).*

Summary of how the substance meets the CMR (Cat 1 or 2), PBT or vPvB criteria, or is considered to be a substance of an equivalent level of concern

Diisobutyl phthalate (DIBP) has been classified as toxic to reproduction (Repr. Cat. 2 and Cat. 3) according to Directive 67/548/EEC by Commission Directive 2009/2/EC amending, for the purpose of its adaptation to technical progress, for the 31st time, Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. According to Article 57 (c) of Regulation 1907/2006 (the REACH Regulation) substances meeting the criteria for classification as toxic for reproduction category 1 or 2 in accordance with Directive 67/548/EEC may be included in Annex XIV.

The classification as Repr. Cat. 2 and Cat. 3 will also be included in Annex VI, part 3, Table 3.2 (the list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008 by a Commission Regulation amending, for the purposes of its adaptation to technical progress, for the first time Regulation 1272/2008. This Commission Regulation was adopted on 10 August 2009 (publication and entry into force of this Regulation is expected to be in September/October 2009).

The corresponding classification for DIBP in Annex VI, part 3, Table 3.1 of Regulation (EC) No 1272/2008 (list of harmonised classification and labelling of hazardous substances) will be Repr. 1B.

Registration number(s) of the substance or of substances containing the substance:

Not available.

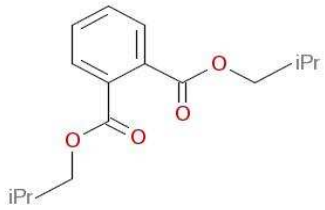
JUSTIFICATION

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Chemical Name:	Diisobutyl phthalate (DIBP)
EC Name:	Diisobutyl phthalate
CAS Number:	84-69-5
IUPAC Name:	Bis(2-methylpropyl)benzene-1,2-dicarboxylate

1.2 Composition of the substance

Chemical Name:	1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester
EC Number:	201-553-2
CAS Number:	84-69-5
IUPAC Name:	Bis(2-methylpropyl)benzene-1,2-dicarboxylate
Molecular Formula:	$C_{16}H_{22}O_4$
Structural Formula:	
Molecular Weight:	278.35 g/mol
Typical concentration (% w/w):	99
Concentration range (% w/w):	98 – 100

1.3 Physico-chemical properties

REACH ref Annex, §	Property	IUCLID section	Value	[enter comment/reference or delete column]
VII, 7.1	Physical state at 20°C and 101.3 kPa	4.1	Colourless, clear , mostly odourless viscous liquid	
VII, 7.2	Melting/freezing point	4.2	-37 °C	Woodward (1988)
VII, 7.3	Boiling point	4.3	320 °C	Härtel (1985)
VII, 7.5	Vapour pressure	4.6	0.01 Pa at 20 °C	Potin-Gautier et al. (1982)
VII, 7.7	Water solubility	4.8	20 mg/l at 20 °C	Leyder and Boulanger (1983)
VII, 7.8	Partition coefficient n-octanol/water (log value)	4.7	logPow: 4.11	Leyder and Boulanger (1983)

Table 1: Summary of physico- chemical properties

2 MANUFACTURE AND USES

Not relevant for this type of dossier.

3 CLASSIFICATION AND LABELLING

3.1 Classification according Directive 67/548/EEC and in Annex VI of Regulation (EC) No 1272/2008

Diisobutyl phthalate (DIBP) was classified according to Directive 67/548/EEC by the 31st Adaptation to Technical Progress (31st ATP; Commission Directive 2009/2/EC)[1] as follows:

Index Number: 607-623-00-2

Repr. Cat. 2; R61 (May cause harm to the unborn child)
Repr. Cat. 3; R62 (Possible risk of impaired fertility)

Specific concentration limits:
C ≥ 25 %: T; R61-62
5 % ≤ C < 25 %: Xn; R62.

This classification will be included in Annex VI, part 3, Table 3.2 (the list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008[2] by a Commission Regulation amending, for the purposes of its adaptation to technical progress, for the first time Regulation 1272/2008. This Commission Regulation has been adopted on 10 August 2009 (publication and entry into force of this first ATP is expected to be in September/October 2009[3]).

According to the first ATP to Regulation (EC) No 1272/2008, the corresponding classification in Annex VI, part 3, Table 3.1 of this Regulation (EC) No 1272/2008 (list of harmonised classification and labelling of hazardous substances) will be as follows:

Repr. 1B, H360Df (May damage the unborn child. Suspected of damaging fertility.).

---

1 COMMISSION DIRECTIVE 2009/2/EC of 15 January 2009 amending, for the purpose of its adaptation to technical progress, for the 31st time, Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances.

2 Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006

3 Pursuant to Article 53(1) of Regulation 1272/2008 this Commission Regulation was adopted in accordance with the regulatory procedure with scrutiny involving both the Council of the EU and the European Parliament.

3.2 Self classification(s)

none

4 ENVIRONMENTAL FATE PROPERTIES

Since this is a dossier targeted to the identification of DIBP as a CMR substance, environmental fate properties have not been considered.

5 HUMAN HEALTH HAZARD ASSESSMENT

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Not relevant for this type of dossier.

5.2 Acute toxicity

Not relevant for this type of dossier.

5.3 Irritation

Not relevant for this type of dossier.

5.4 Corrosivity

Not relevant for this type of dossier.

5.5 Sensitisation

Not relevant for this type of dossier.

5.6 Repeated dose toxicity

5.6.1 Repeated dose toxicity: oral

In toxicity studies with repeated oral application the male reproductive system was identified as one and most important target organ of toxicity for DIBP. Available early feeding studies in experimental animals revealed reproductive effects in adult males (e.g., decreased testes weight and reduced sperm production in rats) at relatively high oral doses. Sub-acute studies with rats and mice, and sub-chronic studies with rats and dogs are available. Although these studies were not comparable to guideline studies and not in conformity with GLP they point clearly out the critical organs of toxicity for DIBP – the male sex organs. The distinctions in study design compared to published guidelines include e.g., no precise data on strain, number and sex of the used animals; in some studies only animals of one sex were tested.
Similar studies with the correspondent monoester, mono-iso-butyl phthalate (MIBP) to which DIBP is hydrolysed are also available and summarised below. MIBP is likely to be the major metabolite of DIBP (Mentlein and Butte, 1989).

In albino rats (strain unknown), a feeding study over a period of four months is reported by Hodge (1954). Body weights and haematological parameters were measured. Organ weights were determined at autopsy. Livers and kidneys were examined histologically. Groups of rats (5/sex/group) were fed 0, 0.1, 1.0 and 5.0% DIBP in the diet. These dose levels were equivalent to 0 or to about 70, 700 and 3500 mg/kg bw/d in both sexes (calculated on an assumed daily food intake of 7% of the body weight). Retarded growth was observed at dosages of 1.0% and above DIBP in feed. Significantly decreased body weights were observed in both sexes at 5.0% (decrease up to 43% for males and 13% for females). The intake of 5.0% DIBP caused slight reduction in red blood cell counts in males and in haemoglobin values in both sexes. Both absolute and relative testes weights were considerably reduced in the 5.0% group. No statistical analyses were conducted but

reductions were noted to approximately 30% and 50% of control values respectively. Absolute and relative liver weights were raised in the 5.0% groups of both sexes. For males, absolute weights were increased by 5%; relative weights by 80%. For females, absolute weights were increased by 40%; relative weights by 60%. Pathological examinations of liver and kidney were unremarkable.

Hodge (1954) also reported on a feeding study in dogs. One male and one female dog (species unknown) were fed with DIBP via diet at a daily rate of 0.1 ml/kg feed and 2.0 ml/kg feed respectively (equivalent to about 2.6 mg/kg bw/d and 51.9 mg/kg bw/d, calculated on an assumed daily food intake of 25 g/kg bw) for a period of two months. Weight loss was noted in the female dog at the last three treatment weeks. No abnormality was detected in the haematological and urine analyses as well as in gross pathology in both sexes. Organ weight assessment revealed an increase in relative liver weight compared to historical controls in female dog, no histological abnormalities in the liver were observed. In the male dog given 2.6 mg/kg bw/d DIBP, histological examination revealed abnormally few matured sperm in the testes.

To evaluate the effects of DIBP on the testes one week feeding toxicity studies in male rats and mice were performed, especially testosterone and zinc concentrations in the testes as an important role in the maintenance of testicular function were examined.
Feeding a diet containing 2.0% (approximately 1500 mg/kg bw/d, calculated on an assumed daily food intake of 7% of the mean body weight of 108 g) of DIBP to 10 male rats (JCL: Wistar, 5 weeks old) resulted in significantly decreased zinc concentrations in the testes and liver. Testosterone concentrations in the testes were increased but appeared normal in the serum. The testes of DIBP-treated rats were reduced in size when compared to controls, and organ weight assessment revealed significantly ($p<0.05$) decreased absolute and relative testicular weights in these rats. Microscopy indicated marked inhibition of spermatogenesis and desquamation of spermatocytes (Oishi and Hiraga, 1980c).
In a comparable study in male mice zinc and testosterone concentrations in tissues were determined, and body and organ weights of testes, liver and kidneys were evaluated, however microscopy was not performed. Administration of 2.0% (approximately 2000 mg/kg bw/d, calculated on an assumed daily food intake of 10% of the body weight) of DIBP in the diet to 10 young male mice (JCL: ICR) revealed significantly decreased zinc concentrations in the testes. The concentration of testosterone in the testes of DIBP-treated mice was not different from control values. The relative weights of the testes and liver of DIBP-treated mice were significantly higher, but the absolute testis weight was not different from control values (Oishi and Hiraga, 1980b).

The purpose of studies with MIBP was to discover whether phthalic acid monoesters including their metabolites have similar effects to their diesters regarding effects on the testes and alterations in zinc and testosterone concentrations.
Administration of 2.0% MIBP (corresponding to total intake of 2300 mg/kg bw/d) in the diet to 10 male rats (JCL: Wistar, 5 weeks old) for 7 days resulted in significantly suppressed food consumption throughout the experimental period, depressed body weight gains (69% of controls), and significantly decreased absolute and relative testes weights (60% of controls). Examination on the concentration of zinc in the testes, liver, kidneys and serum showed significantly decreased values in the testes and liver (60% and 90% of control values). Testosterone concentrations in the testes and serum were significantly increased by 260% and 160% of control values. Microscopy was not performed in this study (Oishi & Hiraga, 1980d).

In a further rat study 800 mg/kg bw/d MIBP was administered by gavage to young male Sprague-Dawley rats (80-100 g) daily for six days. MIBP was given in aqueous solutions as the ammonium salt (pH 6.0). Control animals received an equivalent amount of ammonium chloride (pH 6.0).

Liver, kidneys, testes and accessory sex organs were weighed, and testes and accessory sex organs were examined by light microscopy. Additionally zinc metabolism was examined in 9 rats received [^{65}Zn]Cl_2 (50 µCi/kg body wt.) i.p. 48h prior to treatment with MIBP for 4 days. The ^{65}Zn content was determined in liver, kidney and testes. Urinary ^{65}Zn excretion was examined over a 24-h period following 4 days of treatment. Treated rats developed markedly reduced absolute and relative testes weights (73%, P<0.001), and lowered seminal vesicle weights (not significant) compared to control values. No differences were evident from prostate weights. Microscopy revealed in all six examined animals marked testicular atrophy of the majority of the seminiferous tubules with a diminution of both spermatocytes and spermatogonia. In all instances the lesions were bilateral in origin. No abnormalities were detected in sections of prostate or seminal vesicles. The zinc metabolism was adversely altered by significantly increasing urinary zinc excretion concomitant with decreased ^{65}Zn testicular content and elevated renal ^{65}Zn content (Foster et al., 1981).

In a mice study body weights and organ weights of testes, liver and kidneys were evaluated; and zinc concentration in testes, liver and kidneys was determined, and testosterone concentration in the testes. Feeding of 2.0% (approximately 2000 mg/kg bw/d, calculated on an assumed daily food intake of 10% of the body weight) MIBP in the diet to 10 male mice (JCL: ICR, 5 weeks old) for 7 days resulted in significantly increased relative liver and testes weights associated with decreased body weight, whereas the absolute weights did not differ from control values. The average zinc level in the testes of MIBP-treated mice was significantly lower than the control value and did not differ in liver and kidneys. Testosterone concentration in the testes was significantly decreased (Oishi & Hiraga, 1980a).

5.6.2 Repeated dose toxicity: inhalation

5.6.3 Repeated dose toxicity: dermal

5.6.4 Other relevant information

5.6.5 Summary and discussion of repeated dose toxicity:

DIBP induces microscopic testicular atrophy associated with markedly reduced testes weights in rats and alterations in zinc and testosterone concentrations in rats and mice. Dietary administration of MIBP (the correspondent monoester, mono-iso-butyl phthalate to which DIBP is hydrolysed) induced also severe atrophy of the testes, high testosterone concentration in the testes, and low zinc concentration. Testicular effects have been demonstrated in adult male rats after repeated oral exposures to high doses of DIBP or MIBP. Decreased absolute and relative testes weights were seen in rats fed a diet containing 3500 mg/kg bw/d DIBP for a period of four months, but also in 5-week-old rats fed 2.0% (approximately 1500 mg/kg bw/d) DIBP in their diet for seven days. Markedly reduced absolute and relative testes weights were also observed in rats treated with ≥ 800 mg/kg bw/d MIBP for 7 days. In mice, treatment with approximately 2000 mg/kg bw/d DIBP or MIBP in the diet for the same duration of treatment did not show any effect on absolute testes weights but resulted in significantly increased relative testes weight.

Marked inhibition of spermatogenesis and desquamation of spermatocytes were observed in 5-week-old rats fed 2.0% (approximately 1500 mg/kg bw/d) DIBP in their diet for seven days. Diminished sperm was noted in a study used one adult dog given 2.6 mg/kg bw/d DIBP in the diet for two months. Severe testicular injury as seen as marked testicular atrophy of the majority of the

seminiferous tubules with a diminution of both spermatocytes and spermatogonia was caused by treatment with 800 mg/kg bw/d MIBP for one week.

The role of zinc and testosterone as elements essential for the maintenance of normal testicular function has been analysed in short term studies with male rats and mice. The examination of DIBP effects on the zinc content in the testes showed related results in both species. In rats and mice significantly decreased zinc concentrations were measured in the testes after feeding of 2.0% DIBP in their diet for seven days. The average zinc level in the testes of rats and mice treated with ≥ 800 mg/kg bw/d MIBP for one week was also significantly decreased. Testicular testosterone concentration was significantly increased in rats fed 2.0% (approximately 1500 mg/kg bw/d) DIBP, and also in rats fed 2300 mg/kg bw/d MIBP in their diet for seven days. No effect on the testosterone content was observed in mice receiving approximately 2000 mg/kg bw/d DIBP for 7 days, but was significantly decreased in mice treated with MIBP for the same study period.

5.7 Mutagenicity

Not relevant for this type of dossier.

5.8 Carcinogenicity

Not relevant for this type of dossier.

5.9 Toxicity for reproduction

5.9.1 Effects on fertility

Whereas no fertility studies (one-, two- or multigeneration studies) could be identified in the current toxicological data base for DIBP, adverse effects on male reproductive organs (testicular toxicity) and on spermatogenesis had been observed during repeat dose toxicity studies with DIBP and with MIBP at relatively high dosages (c.f. 5.6.1 Repeated dose toxicity: oral), indicating that the monoester MIBP to which DIBP is hydrolysed by human and rat hepatic esterases (Mentlein and Butte, 1989) should be considered an active metabolite.

5.9.2 Developmental toxicity

Prenatal developmental toxicity studies

In a comparative study on eight different phthalate esters Singh et al. (1972) treated pregnant Sprague Dawley rats (n = 5/group) with DIBP at single doses of 0.375, 0.75 and 1.25 ml/kg bw (approximately 390, 780 and 1300 mg/kg bw) by intraperitoneal injection on three different days during gestation. Animals of the control groups were either untreated or received a similar volume of distilled water, normal saline or cottonseed oil. The pregnant females were treated on 3 days during gestation (GD 5, 10 and 15) and were sacrificed on GD 20, one day prior to parturition. Ovaries were taken for recording of the numbers of corpora lutea; uterine horns were taken for recording the numbers of resorption sites, and of dead and viable fetuses. Fetuses were weighed and examined for gross malformations. A randomly selected number of fetuses (30-50% of the total) was taken for evaluation of skeletal malformations. Investigation on any maternal parameters is not reported from the study. As a result, there was no difference observed in the number of corpora lutea at any dose level in comparison to the controls. An increase in resorptions (25.8%) was revealed at the high dose level, indicating an embryotoxic potential and leading to a decrease of the

number of live fetuses. At the dose level of 0.75 mL/kg bw 2 out of a total of 52 fetuses were found dead, however, at the low and high dose level only life fetuses were recorded. The average weight of fetuses was reduced in comparison to controls at all dose levels. Gross abnormalities (not further specified) were observed in two fetuses, however at the dose level of 0.75 ml/kg bw only and an increased incidence in skeletal abnormalities was reported for the high dose level (not further specified).

In a further study (Borch et al., 2006; cited in: Boberg et al., 2008) mated female Wistar rats (n=8/group) were gavaged from GD 7 until GD 19 or until GD 20/21 with either vehicle (corn oil) or 600 mg/kg bw/d of DIBP (purity 99%), when they were sacrificed and their male offspring evaluated. At sacrifice on GD 19 five dams from the control and six dams from the treated group provided litters and at sacrifice on GD 20/21 six dams from the treated group provided litters. Anogenital distance (AGD) was measured in all fetuses, fetuses were decapitated and their trunk blood collected, and from males testes removed for histopathology and for immunohistochemistry, for measurement of testosterone production ex vivo, respectively measurement of testosterone content. Administration of DIBP resulted in statistically significant reduction in AGD in male pups (and increased AGD in female pups) at GD 20/21 together with 10 % reduction in bodyweights of male and female fetuses and in a significant reduction in testicular testosterone production and testicular testosterone content in the male offspring at GD 20/21. Histopathological investigations revealed testes pathology as seen with other phthalates, in particular clustering of small Leydig cells on GD19 or GD20/21 and vacuolisation of Sertoli cells on GD 20/21. Immunohistochemistry revealed reduced staining for StAR and P450scc, indicative for reduced expression of these two proteins and thereby reduced capacity of the testicular steroid synthesis. Further results from this study were reported by Boberg et al. (2008), who quantified levels of insulin, leptin, MCP1, IL-1B, PAI-active, IL6, and TNFα in pooled samples of plasma. In addition, livers, adrenals and testes tissue from the male fetuses and ovaries from the females had been used for gene expression (mRNA expression) analysis and for steroid hormone measurements (estradiol, testosterone). Treatment with DIBP had resulted at GD 21 in statistically significant reduction of protein levels of insulin and of leptin, whereas no alterations were seen in plasma levels of MCP1, IL-1B, PAI-1 active, IL6 or TNFα. Gene expression analysis on genes involved in steroid synthesis revealed reduced testicular mRNA levels of SR-B1, StAR, P450c17, P450scc and Insl-3 at GD 19 and GD 21. In addition testicular SF-1 mRNA levels were reduced on GD 19, whereas no alterations were seen for testicular mRNA levels of aromatase or PBR. In the ovaries of DIBP treated animals an increase in mRNA levels of aromatase was revealed at GD 21. Gene expression analysis on PPARα and on PPARγ revealed significantly reduced mRNA levels of PPARα in livers and testes of DIBP exposed males at GD 19 but not at GD 21. PPARγ mRNA levels were very low in both testes as well as livers and appeared unaltered by DIBP treatment. In the ovaries of DIBP treated animals no alterations were seen in the expression of ERα, ERβ, PPARα, or PPARγ. Besides reductions in mRNA levels there were also indications for reduced protein levels of P450c17 and of PPARγ in the Leydig cells of DIBP treated animals at GD 19 and GD21 (evidenced from reduced immunostaining intensity).

In a dose-range finding study on Sprague-Dawley rats, DIBP was administered to pregnant animals (10-14 animals per treatment group) by gavage at doses of 0 (olive oil), 250, 500, 750 and 1000 mg/kg bw/d (Saillenfait et al., 2005) on GD 6-20. Maternal body weights and clinical signs were recorded. Dams were euthanised on GD 21, and the uterine contents were evaluated for number of implantations, resorptions, fetal deaths, and live fetuses. All live fetuses were submitted to external examination and to internal gross examination of the reproductive tract. Maternal body weight gain was transiently depressed on GD 6-9 at the two higher dose levels. However, the weight gains during GD 6-21 corrected for uterine weight were comparable across groups. A marked increase in

the number of resorptions of 38% and of 61% was observed at the 750 and 1000 mg/kg bw/d dose level. A dose-related reduction in fetal body weight was observed amounting to 21% at 1000 mg/kg. Gross internal examination of the reproductive tract revealed undescended testes in 56% and 70% of the male fetuses at 750 and 1000 mg/kg. No further visceral or skeletal examinations were conducted.

In a further guideline according prenatal toxicity study on Sprague-Dawley rats, DIBP was administered to pregnant animals (23-24 animals per treatment group) by gavage at doses of 0 (olive oil), 250, 500, 750 and 1000 mg/kg bw/d on GD 6-20 (Saillenfait et al., 2006). Endpoints included in addition were determination of the degree of transabdominal testicular migration (TTM). There were no maternal deaths. Signs of transient maternal toxicity were observed, as evidenced by reduction in body weight gain, at the beginning of treatment (GD 6-9) at 500 mg/kg bw/d and higher doses, however, overall weight gain corrected for gravid uterus was not different from controls at the end of gestation. No changes could be observed for maternal food consumption, pregnancy rate or number of implantations. The incidences of resorptions were statistically significantly increased to 28% at 750 mg/kg bw/d and to 59% at 1000 mg/kg bw/d. Mean fetal body weight was statistically significantly reduced at 500 mg/kg/d and higher doses amounting to a decrease of 24% -26% at 1000 mg/kg/d in comparison to controls. The incidence of total external malformations (neural tube closure defects, anophthalmia) and of total visceral malformations (urinary tract and vascular defects) was statistically increased at 750 and 1000 mg/kg bw/d. Skeletal evaluations revealed malformations primarily of the axial column with the incidences of fused sternebrae statistically significantly increased at 750 and 1000 mg/kg bw/d and variations (delayed ossification and supernumerary ribs) at 750 and 1000 mg/kg bw/d with supernumerary ribs in 95% of the fetuses of the 1000 mg/kg group. Visceral variations involved mainly the urinary tract with statistically significantly increased incidences of ureter variations in the 1000 mg/kg group and the male reproductive system. Unilateral or bilateral undescended testes occurred at 500 mg/kg/d and was significantly increased at 750 mg/kg/d (in 30/55 male fetuses and in 16/20 litters) and at 1000 mg/kg bw/d (in 30/34 male fetuses and in 16/17 litters). In addition the degree of transabdominal descent was significantly impaired at 500 mg/kg/d with about two third of the testes located in the upper half of the abdominal cavity at the 1000 mg/kg dose group. Thus, it appeared that alterations of the male reproductive system occurred at lower doses than those producing structural malformations/variations and embryotoxicity. No evidence of embryo or fetal effects was found at the 250 mg/kg dose level. Therefore, a NOAEL/developmental toxicity of 250 mg/kg/d can be derived from the study.

In a further study on Sprague-Dawley rats, which was designed to provide dose-response information on the effects of a series of individual phthalates on fetal testosterone production and on the use of the data obtained for the prediction of effects of phthalate mixtures on fetal testosterone production, DIBP was administered to pregnant animals (5-8 animals per treatment group) by gavage at doses of 0 (corn oil), 100, 300, 600, and 900 mg/kg bw/d on GD 8-18 (Howdeshell et al., 2008). Maternal body weights were taken on GD 8 and on GD 18 at sacrifice, when the uterus was removed and the number of fetuses (live and dead) and resorptions were counted and recorded. The total number of implantations was calculated by adding together the number of live and dead fetuses with the total number of resorptions. Fetal mortality was calculated by adding together the number of resorptions and dead fetuses then divided by the total number of implantations. Testes from three males/dose group (2 replicate determinations in individual testes) in were used for investigation of ex vivo testis testosterone production. Maternal body weight gain was reduced from 73 g in controls to 48 and 43 g in the 600 and 900 mg/kg/d dose group.
DIBP-induced complete litter loss in 1/5 dams at 900 mg/kg/d, and induced greater than 50% resorptions in 2/5 dams at 900 mg/kg/d and in 1/5 dams at 600 mg/kg/d resulting in increased

percentages of fetal mortality of 17% at 600 mg/kg/d and of 59% at 900 mg/kg/d as compared to 1.3% in the controls. It is reported, that many of the testes collected from DiBP fetuses at dosages of 600 and 900 mg/kg/d were smaller, mucinilagous, and/or located higher in the abdominal cavity. The functional assay on testes ability for hormone production revealed that fetal testicular testosterone production was statistically significantly ($p<0.001$) reduced at dosages of 300 mg/kg/d or higher. The overall results indicated that DIBP (as well as DBP and BBP) was of equivalent potency to DEHP at reducing fetal testosterone production. Dosage levels reducing fetal testosterone production were about one-half to one-third of that required to increase fetal mortality, indicating changes in fetal testicular testosterone production to be a sensitive parameter. Based on statistically significantly lower fetal testosterone production at 300 mg/kg/d a NOAEL of 100 mg/kg bw/d can be derived from this study.

A further guideline according prenatal toxicity study on Wistar rats (BASF, 2003; cited in Saillenfait and Laudet-Hesbert, 2005) with dietary administration is indicated in the data base, for which the study report is not available to the rapporteur. It is reported that a decrease in fetal weights and an increase in skeletal variations was observed in rats that had ingested 942 mg/kg DIBP with their diet during pregnancy.

Postnatal developmental toxicity studies

In a study on Sprague-Dawley rats, which was performed to determine whether in utero exposure to DIBP would induce permanent and dose-responsive alterations of male reproductive development, DIBP was administered to pregnant animals (11-13 animals per treatment group) by gavage at doses of 0 (olive oil), 125, 250, 500, and 650 mg/kg bw/d on GD 12-21 (Saillenfait et al., 2008). Doses were based on an unpublished preliminary study in which 625 mg DIBP/(kg day) on GD 12-21 caused reproductive tract malformations in male offspring and had no effects on litter size or pup survival. Litters of the definite study were examined as soon as possible after birth to determine the number of viable and stillborn pups. Pup body weights were recorded on PND 1, 4, 7, 14 and 21. AGD was measured on PND1 and litters culled to 10 pups on PND 4. All pups were examined for the presence of areola and/or nipples on the ventral surface of the thorax on PND 12-14. At weaning on PND 21 three to four male pups from each litter were randomly selected and retained and unselected pups sacrificed and submitted to internal examination. After weaning the dams were sacrificed and the number of implantations recorded from their uteri. All retained males were examined for preputial separation (PPS) and individual body weights recorded at acquisition. Adult males were necropsied on PND 76-86 (two males in each litter) or on PND 111-122 (the remaining males in each litter). They were examined for the presence of areolas and/or nipples on the ventral surface of the thorax, for gross abnormalities of external and internal genitalia, and for position of testes. Testes, epididymides, seminal vesicles (with the coagulating glands and seminal fluid), and prostate were weighed. Histopathology was conducted on testes and epididymides of all DIBP animals necropsied on PND 76-88. No differences in maternal body weight gain were observed between the controls and the treatment groups. All dams delivered live pups. Post-DIBP implantation loss, litter size, sex ratio, and pup survival to PND 4 and PND 21 were unaffected by treatment. AGD measured on PND 1 was dose-dependently significantly reduced in male pups from 250 mg DIBP/(kg day) to the higher doses with or without adjustment for body weight. The decrease amounted to 11% at 250 mg DIBP/(kg day) and 22% at 625 mg DIBP/(kg day), compared to controls. AGD of females was not affected at any dose. Pup body weight at PND 1 of both sexes was statistically significantly decreased at 625 mg DIBP/(kg day), and remained lower in comparison to controls in the male pups at weaning. During the post weaning period mean body weights of the offspring were lower than controls at 500 and 625 mg DIBP/(kg day) (6-8% and 10-12%, respectively). On PND 12-14 or at adult necropsy retained areolas and/or nipples were

apparent in males at 250 mg DIBP/(kg day) and their incidence increased with dose. No such effects were observed in animals from vehicle controls or the 125 mg DIBP/(kg day) treated group. Acquisition of PPS was delayed by approximately 4 days at 500 mg DIBP/(kg day). Evaluation of PPS was precluded in half of the males at the high dose by presence of hypospadias. Mature males displayed severe malformations (hypospadias with exposed os penis in the more severely affected animals, and non-scrotal testis) at the two high doses. Non-descended testes were always located in the inguinal or supra-inguinal area; none were in the intra-abdominal position. Markedly underdeveloped (less than 10% of control weight) or absent testes and/or epididymes were seen in 2%, 16% (7 males from 5 litters), and 13% (5 males from 4 litters) of the animals in the 250, 500 and 625 mg /(kg day) dose groups. At sacrifice (PND 76-86, resp. PND 111-122) organ weights of the testes, epididymes, seminal vesicles and prostate were significantly reduced (with or without body weight as covariate) at 500 and 625 mg DIBP/(kg day). These reductions amounted to 39-59% for the testes and the epididymes, and 28-33% for the seminal vesicles and the prostate. Histological examinations revealed testicular damage in all DIBP treated groups with moderate or severe degeneration of seminiferous tubules (including Sertoli cell only tubules). The lesions were uni- or bilateral and associated with oligospermia or total azoospermia in the corresponding epididymides. Based on these observations a NOAEL/developmental toxicity could not be determined. Therefore, a LOAEL/developmental toxicity of 125 mg DIBP/kg bw/day can be derived from this study.

DIBP was further evaluated in a Chernoff-Kavlock screening assay in which CD-1 mice (50 dams/group) were gavaged on GD 6-13 with a single dose level of 4000 mg/kg bw/d or corn oil (Hardin et al., 1987). Dams were allowed to litter and a postnatal evaluation was conducted. At that dose, no pregnant dams gave birth to a live litter and 27/50 exposed dams died.

5.9.3 Human data

In the attempt to explore whether prenatal exposure to phthalates would be reflected in postnatal performance of genital parameters concentrations of 11 maternal urinary phthalate monoesters were determined in spot urine samples taken prenatally during pregnancy and associated to parameters such as anogenital index (AGI) – a biomarker suspected to be indicative of androgen action also in humans - and testicular descent in the male infants in a cohort of 85 mother-son pairs (Swan et al., 2005). In this investigation maternal urinary MIBP concentration was found to be inversely related to AGI, and that in general the boys classified as having a short AGI (AGI below 25th percentile for age) also had a higher prevalence of concomitant cryptorchidism. Although of limited value, due to the small number of subjects (n=85) and to other shortcomings (e.g., concentrations of phthalate metabolites in spot urine samples may not be representative for and adequately reflect maternal exposure during pregnancy), data of this study may support the hypothesis that prenatal phthalate exposure at environmental levels may affect male reproductive development also in humans. It should be noted, in addition, that little is known on the normal variation of AGD in human infants to adequately interpret the findings on AGI values lower than expected and that any long-term clinical implications of a shorter than expected AGD in humans has not yet been revealed.

5.9.4 Other relevant information

Mode of action – in vitro assays

DIBP was negative for oestrogenic activity in a yeast two-hybrid assay (Nishihara et al., 2000) and showed extremely weak oestrogenic activity in a recombinant yeast assay and in cell proliferation assays with MCF-7 and ZR-75 cells (Harris et al., 1997). In a commercial Ligand Screening Assay DIBP (up to 10^{-5}M) had no binding affinity for the oestrogen receptor α or β in vitro (Toda et al.,

2004). In a reporter gene assay DIBP was found to induce oestrogen receptor hERα-mediated oestrogenic activity (at 10^{-5}M) and possess antiandrogenic activity in vitro but showed no activity towards hERβ in CHO-K1 cells (Takeuchi et al., 2005).

5.9.5 Summary and discussion of reproductive toxicity

The available data base has been evaluated for the toxic potential of DIBP adverse to reproduction and development. DIBP was found to adversely affect the reproductive organs in adult males in experimental studies which may affect their fertility. DIBP was also found to be a developmental toxicant. The results of these evaluations are reflected in the classification as Repr. Cat 3; R62 and Repr. Cat 2; R 61 according to directive 67/548/EEC.

Any generation or fertility studies are not available in the toxicological data base for DIBP. However, adverse effects on male reproductive organs (testicular toxicity) and on spermatogenesis had been induced in studies with young adult male rats and mice after repeated oral administration of DIBP at relatively high dosages. Similar effects were also revealed after treatment with MIBP, the major monoester metabolite of DIBP. A NOAEL has not been established from theses studies for testicular toxicity in adult males. Further, the data base lacks information for evaluation of any effects on female fertility or effects on the female adult reproductive system.

Studies related to developmental toxicity revealed embryotoxic, fetotoxic and teratogenic properties of DIBP. In a guideline according study embryolethality in terms of an increase in resorptions, fetal growth retardation in terms of significantly reduced fetal body weight and structural defects were observed in the skeletal system and in various organ systems including the male reproductive system at dosages ($\geq$ 500 DIBP mg/kg bw/d) without signs of maternal toxicity, respectively early transient maternal weight gain effects only. DIBP exposures focused to a sensitive period (GD 12-21) caused preferential and permanent effects on the male reproductive system at lower doses than those inducing embryolethality and malformations not related to the reproductive system. Impact on AGD at birth and areola/nipple retention in male progeny during early postnatal live ($\geq$ 250 mg/kg bw/d) and changes in testicular histopathology of in utero exposed male progeny ($\geq$ 125 mg/kg bw/d) appeared to be sensitive markers for DIBP induced effects on the development of the male reproductive system. Changes in fetal testicular testosterone production, however, revealed to be the most sensitive parameter for the adverse effects of DIBP on development of the male reproductive system, based on which a NOAEL/developmental toxicity of 100 mg/kg bw/d. The pattern and types of malformation of the male reproductive system observed with DIBP did not differ from those seen after treatment with DNBP, principally consisting of cleft prepuce, hypospadias, and inguinal or supra-inguinal testis. Incidences of hypospadias and of undescended testes were lower for DIBP when compared for equal dosages. However, in reducing fetal testosterone production DIBP was of equivalent potency as DEHP, DBP and BBP, phthalates which are also potent reproductive toxicants.

The structures affected by in utero exposure to DIBP are indicative of an antiandrogenic mode of action. In particular, the development of dihydrotestosterone-regulated tissues (e.g. areolas/nipples, external genitalia including AGD and hypospadias) were severely affected. DIBP had also marked effects on the final inguinoscrotal descent, which is known to require androgens. The changes in the androgen-dependent endpoints induced by DIBP treatment are congruent with the findings of lowered fetal levels of testosterone and changes in the expression of several genes in the cholesterol uptake, transport and testicular testosterone biosynthesis in other studies. Although phthalates do not act as classical antiandrogenic chemicals by binding to the androgen receptor, they obviously

have the same effects of blocking androgen-action at the target tissue and therefore may be considered as acting antiandrogenic.

5.10 Other effects

Not relevant for this type of dossier.

5.11 Derivation of DNEL(s) or other quantitative or qualitative measure for dose response

Not relevant for this type of dossier.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Not relevant for this type of dossier.

7 ENVIRONMENTAL HAZARD ASSESSMENT

Since this is a dossier targeted to the identification of DIBP as a CMR substance, no environmental hazard assessment has been carried out.

8 PBT, VPVB AND EQUIVALENT LEVEL OF CONCERN ASSESSMENT

Since this is a dossier targeted to the identification of DIBP as a CMR substance, no PBT, vPvB and equivalent level of concern assessment has been carried out.

INFORMATION ON USE, EXPOSURE, ALTERNATIVES AND RISKS

1 INFORMATION ON EXPOSURE

1.1 Production volumes

Concerning the actual production volume of DIBP there are no extensive data available. A relevant search led only to the information over a world wide production of DBP (dibutyl phthalate)/DIBP of approximately 450,000 tpa (www.tecnon.co.uk/gen).
In ESIS (European chemical Substances Information System; http://ecb.jrc.ec.europa.eu/esis/) DIBP is characterized as HPVC (High Production Volume Chemical; quantity exeeds 1000 tpa). Companies in Austria, Germany, Italy, Spain and UK manufacture or import DIBP. In an authorized IUCLID data sheet (2000) a quantity of DIBP is indicated from 10,000 to 50,000 t.
From the current version of the Nordic product data base it can be seen that DIBP had a wide dispersive use in the period 2000 – 2006 (http://195.215.251.229/fmi/xsl/spin/SPIN/maininfo.xsl).

The most current accessible data for the production of DIBP in Germany concern the year 2002 (IUCLID5: see '3.2 estimated quantities'). Accordingly the companies HÜLS AG and BASF AG produced 1,000 – 5,000 tpa respectively 10,000 - 50,000 tpa DIBP.
Information on earlier production of DIBP in Germany is presented in the BUA Report 201 (1997). The report informed about the fact that the companies BASF AG and HÜLS AG are the only producers of DIBP in Germany. The national production volume of DIBP was below 10,000 t in 1994 (BASF, 1996; Hüls, 1995). No precise data were given. The Federal Bureau of Statistics (Statistisches Bundesamt, 1994) specified foreign trade figures for DIBP only together with other substances. Thus, a total of 1,417 t DIBP plus DBP were imported into Germany in 1993 and 10,547 t exported. A national consumption of below 5,000 tpa was estimated considering the import and export quantities.

On a common online platform (http://www.chemcompass.de/) of the German Chemical Industry Association (VCI) and the German Association of Chemical Trade and Distribution (VCH) the following companies are listed, which produce DIBP in Germany at present: ABCR Dr. Braunagel GmbH & Co. KG, Alfa Aesar GmbH & Co. KG, BASF SE, Evonik Oxeno GmbH, HCH Highchem Hamburg GmbH, Henkel AG & Co. AG, Merck KGaA, Merck Schuchardt OHG, Stockmeier Chemie, Stockmeier Chemie GmbH & Co. KG. No information about the production volumes is given.

1.2 Information on uses

Consumer Exposure
DIBP is used as a specialist plasticizer (Hazardous Substances Data Bank (HSDB), http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB) and frequently as a gelling aid in combination with other plasticizers and as plasticiser for nitrocellulose, cellulose ether and polyacrylate and polyacetate dispersions. Due to similar application properties it may be used as a substitute for Di-n-butyl phthalate (DBP) (Bononi and Tateo, 2009; DIBP Information Centre, http://www.-facts.com/index.asp?page=1).

DIBP has been detected in many consumer products frequently used by children like crayons (Stiftung Warentest, 2008a), bar ends of run bikes (Stiftung Warentest, 2008b), erasers and school

bags (Danish EPA, 2007). In a Chinese study DIBP has been identified in consumer products such as suckers, plastic spoons and forks, boxes for microwave ovens, milk package bags, disposable cups, plates and bowls. The concentrations of DIBP in those products ranged from 0.01 up to 7.8 mg/kg (Shen, 2005).

In the context of the German National Surveillance Plan DIBP has been identified in 7 dolls or figures (BVL, 2008a). In a survey on 8 selected toys and childcare products produced from foam plastic, DIBP concentrations ranged between 2.8 and 1800 mg/kg (Danish EPA, 2006).

DIBP was found in 20/36 perfumes with concentrations ranging from 0.2 - 38 mg/kg (SCCP, 2007). In the report of Wormuth et al. (2006) the dermal exposure route resulting from contact of DIBP to several cosmetic products is considered to be negligible.

Maximum concentrations in products are not yet available but be expected by the authorisation process.

Consumer exposure via food consumption
DIBP is used as a plasticiser in dispersion glues and printing inks for paper and packaging. Concentrations of up to 5 mg/kg have been found in food packaged in cartons. Fat-containing, powder and fine grain foods like rice, baking mixtures or breadcrumbs in paper and board packaging made of recycled fibres were particularly affected. The German Federal Institute for Risk Assessment (BfR) together with the Federal Environment Agency (UBA) and manufacturers of paper and board discussed this problem at a special meeting of the working group “Paper and board” and proposed initial measures (BfR, 2007). In follow-up surveys on food packaged in paper and cartons, DIBP was detected in most samples. In 8.7% of the testet samples the migration limit of 1mg/kg, recommended by BfR, was exceeded with a maximum concentration of 29.4 mg/kg in popcorn for microwave. The highest concentration detected in packaging material was 7055.3 mg/kg (BVL, 2008b).

DIBP has been detected in 11 bottled water samples with concentrations ranging between 0.191 µg/l and 0.353 µg/l (Cao, 2007), and in packed food like cheese, bread and hazelnuts (Pfordt, 2004). In a dietary study with 30 complete meals in two boarding schools, DIBP in concentrations higher than the blank was found in 8 meal samples ranging from 0.02 mg/kg to 0.07 mg/kg (Bopp and Altkofer, 2009).

An intake assessment of dietary exposure of adults from DIBP based on duplicate diet samples has been made by Fromme et al. (2007), accounting to 42 µg/day (median) and 157 µg/day (P95).

Consumer exposure via house dust and indoor air
Consumer use of DIBP can also be identified by its existence in house dust. DIBP concentrations have been reported by Butte et al. (2008) accounting for 34 mg/kg (median) in house dust and 390 ng/m³ (median) in indoor air. Taking these values, a daily intake of house dust by children of 100 mg and a daily inhalation volume for children of 10m³ (Ausschuss für Umwelthygiene (AUH), 1995), a daily DIBP intake can be calculated of 3.9 µg via inhalation of indoor air and 3.4 µg via house dust intake.

Overall consumer exposure
The internal consumer exposure estimated by Wormuth et al. (2006) by a scenario-based approach accounts for 0.1 to 8 µg/kg BW per day for infants, and 0.05 to 2 µg/kg bw per day in adults. In infants and toddlers about 60 % of the exposure is covered by food, 30% by ingestion of soil/dust

and 10% by inhalation of indoor air. In adults, > 90% of exposure to DIBP occurs via food intake. The rest of < 10 % is due to inhalation of indoor air.

A daily uptake of DIBP ranging between 0.2 and 14.9 µg/kg bw with a median of 1.7 µg/kg BW and a 95th percentile of 5.2 µg/kg BW has been calculated by Fromme et al. (2007) from human urine excretion of MIBP using 399 single measurements in 50 adult volunteers on 6 consecutive days. Based on the urinary excretion Wittassek and Angerer (2007) deduced a median daily uptake in 6-80 year old persons of 1.5 µg/ kg BW, with a maximum of 27.3 µg/kg bw.

Heudorf (2007) has calculated a daily intake of DIBP from urine excretion in 111 6 year old children ranging between 0.3 and 59.4 µg/kg BW with a median of 2.2 µg/kg bw and a 95th percentile of 10.99 µg/kg BW.

In the German Environmental Survey on Children (Kinder-Umwelt-Survey, 2008) the daily intake for DIBP has been calculated in 600 3 -14 year old children applying two different model calculations based on the creatinine-related and the volume-related metabolite concentrations. Daily intakes calculated with the volume-based model were 3.8 µg/kg bw (median) and 12.9 µg/kg bw (P95) and calculated with the creatininine-based model 3.0 µg/kg bw (median) and 9.6 µg/kg bw (P95). The maximum daily intake was 70.8 µg/kg bw (volume-based model) and 33.4 µg/kg bw (creatinine-based model). The percentage of the children exceeding a daily intake of 10 µg/kg bw was 9.1% (volume-based model) and 4.5% (creatinine-based model). A significant correlation between DIBP in house dust and respective metabolites in the urine was found in this study (Becker et al., 2008).

The uptakes in children calculated by urine excretion by Heudorf (2007) and by the German Environmental Survey on Children exceed the mean internal uptakes in 4-10 year old children calculated by Wormuth et al. (2006) by factors of 5 to >7, indicating unknown sources of exposure.

1.3 Restrictions relating to phthalates

Certain phthalates are restricted in toys and childcare articles, in food packaging and food contact material, in cosmetics, medical devices and preparations/mixtures like paints and adhesives.

- **REACH, Annex XVII** (DIBP not included)

The following phthalates are concerned by restriction according to REACH Regulation (EC) No 1907/2006 / Annex XVII: Restrictions on the manufacture; Placing on the market and use of certain dangerous substances; Preparations and articles (no. 51 and no. 52) (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:136:0003:0280:EN:PDF):

no. 51
bis (2-ethylhexyl) phthalate (DEHP, CAS No 117-81-7, EINECS No 204-211-0)
dibutyl phthalate (DBP, CAS No 84-74-2, EINECS No 201-557-4)
benzyl butyl phthalate (BBP, CAS No 85-68-7, EINECS No 201-622-7)

Conditions of restriction
'Shall not be used as substances or as constituents of preparations, at concentrations higher than 0.1% by mass of the plasticised material, in toys and childcare articles[1].

Toys and childcare articles containing these phthalates in a concentration higher than 0.1% by mass of the plasticised material shall not be placed on the market.
The Commission shall re-evaluate, by 16 January 2010, the measures provided for in relation to this point in the light of new scientific information on such substances and their substitutes, and if justified, these measures shall be modified accordingly.'

([1] For the purposes of this point "childcare article" shall mean any product intended to facilitate sleep, relaxation, hygiene, the feeding of children or sucking on the part of children.)

no. 52
di-"isononyl" phthalate (DINP, CAS No 28553-12-0 and 68515-48-0, EINECS No 249-079-5 and 271-090-9)
di-"isodecyl" phthalate (DIDP, CAS No 26761-40-0 and 68515-49-1, EINECS No 247-977-1 and 271-091-4)
di-n-octyl phthalate (DNOP, CAS No 117-84-0, EINECS No 204-214-7)

Conditions of restriction
'Shall not be used as substances or as constituents of preparations, at concentrations higher than 0.1% by mass of the plasticised material, in toys and childcare articles[1] which can be placed in the mouth by children.
Toys and childcare articles containing these phthalates in a concentration higher than 0.1% by mass of the plasticised material shall not be placed on the market.
The Commission shall re-evaluate, by 16 January 2010, the measures provided for in relation to this point in the light of new scientific information on such substances and their substitutes, and if justified, these measures shall be modified accordingly.'

([1]For the purposes of this point "childcare article" shall mean any product intended to facilitate sleep, relaxation, hygiene, the feeding of children or sucking on the part of children.)

- **Directive 76/768 EEC**

According to the Council Directive 76/768/EEC (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1976L0768:20080424:EN:PDF) following regulation is also valid for phthalates: 'The use in cosmetic products of substances classified as carcinogenic, mutagenic or toxic for reproduction, of category 1, 2 and 3, under Annex I to Directive 67/548/EEC shall be prohibited. … A substance classified in category 3 may be used in cosmetics if the substance has been evaluated by the SCCNFP and found acceptable for use in cosmetic products.' (Article 4b)

- **Directive 93/42/EEC**

If medical devices, intended to administer and/or remove medicines, body liquids or other substances to or from the body or intended for transport and storage of such body fluids or substances, contain phthalates which are classified as carcinogenic, mutagenic or toxic to reproduction, of category 1 and 2, in accordance with Annex I to Directive 67/548/EEC, they must be labelled. If the intended use of such devises includes treatment of children or treatment of pregnant or nursing women, the manufacturer must provide among other things (1) a specific justification for the use of these substances, (2) information on residual risk for these patient groups

and, if applicable, (3) information on appropriate precautionary measures. (Annex I, no.7.5; http://ec.europa.eu/enterprise/medical_devices/guide-stds-directives/cons_vers_93-42-eec.pdf)

- **Toys Directive**

According to the new toys directive which was adopted on the 18.12.2008 by the European Parliament the use of mutagenic, cancerogenic and reprotoxic substances (CMR) is forbidden in toys (Annex II, part III, no. 3). As an exception following limit value regulation was transferred for CMR substances of the chemical right (REACH) on toys (Annex II, part III, no. 4): CMR substances can be contained up to 0.5% in toys materials if they are accessible in no form to children (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:170:0001:0037:EN:PDF).

- **Directive 2007/19/EC**

The Commission Directive 2007/19/EC considered restrictions for phthalates in food packing materials which come into contact with food in Annex III (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:091:0017:0036:EN:PDF).

2 INFORMATION ON ALTERNATIVES

Alternatives may be the use of alternative substances as plasticisers, the use of flexible polymers which don't need plasticisers or the use of completely different materials. Depending on the different product groups (e.g. toys, household goods, decorative articles, flooring, cables, wallcovering, medical devices, paints, adhesives, sealants, etc.) specific application conditions have to be taken into account. Therefore discussions on alternatives should be product group specific.

2.1 Alternative substances as plasticisers

Structurally, phthalate esters are characterised by a diester structure consisting of a benzenedicarbolic acid head group linked to two ester chains. The structural characteristics of the ester side chains affect the physicochemical and toxicological properties of the phthalate. Reproductive and developmental toxicity appear to be associated predominantly with phthalates of carbon backbone of C3 up to C6 as known for DIBP, DBP, DPP, BBP, DIHP and DEHP. Alternative substances could be searched for in phthalates with shorter or longer carbon backbone lengths (C1, C2 or >/= C7) or among non-phthalates.

There are some non-phthalate alternative substances (EFSA, 2008; CSTEE, 2004; Heitmann, 2003; Risk & Policys Limited, 2000; Stuer-Lauridsen et al., 2001; TNO, 2001; TNO, 2002):

- adipates, e.g. di (ethylhexyl) adipate (DEHA), diisononyl adipate (DINA),
- citrates, e.g. acetyl tributyl citrate (ATBC),
- cyclohexanedicarboxylic acid esters, e.g. di-(isononyl)-cyclohexane-1,2-dicarboxylate (DINCH),
- terephthalic acid, bis(2-ethylhexyl)ester (DEHT)
- organic phosphates,
- medium chained chloroparaffines (MCCP)

- trimellitates, terepthalates, benzoates, succinates, azelates, sebacates, epoxy plasticisers, alkylsulfonic acid esters, polymeric plasticisers, sorbitol-based plasticisers.

MCCP is a suspected PBT substance, so it can not be recommended for replacement of DIBP. For the other non-phthalate plasticisers there are currently not enough data available for a comprehensive assessment of their eco-/toxicological properties.

2.2 Alternative techniques/materials

Alternative techniques or a combination of alternative techniques with other substitution activities may be a solution. According to the draft risk reduction strategy report on DEHP (KEMI, 2006) several alternative techniques are under development:

- "Grafting in order to incorporate subgroups into the polymer structure. In this way copolymers are created that are flexible in themselves and thus without the need for added plasticisers. […] This technique can only be a possible option for large bulk producers of PVC, who do not need the kind of flexibility in properties/formulations that can be obtained by mixing a standard PVC resin with different plasticisers and other additives."

- "Formulation of PVC with other polymers like EVA and PU. By this technique mixtures of PVC can be obtained with different flexibility without plasticisers."

- "Research about the possibilities to use phthalates fixed within the polymer and not as an additive that can migrate is also taking place."

- Flexible plastics that might be used as alternatives to flexible PVC are polypropylene, polyethylene, ethylene-vinylacetate copolymers (EVA), ethylene propylene diene terpolymers (EPDM), polyurethane (PU) and thermoplastic elastomers.

- Completely different materials than flexible PVC (wood, ceramic, stone, cork, paper, linoleum, caoutchouc non-flexible plastics.) might be considered by producers and also by consumers, e.g. instead of PVC flooring consumers may be decide to have wooden material.

3 RISK-RELATED INFORMATION

OTHER INFORMATION

DIBP meets the criteria for classification as toxic for reproduction category 2 and should therefore included in Annex XIV in accordance with the procedure laid down in Article 58 of the Regulation (EC) No 1907/2006 (REACH).

The toxicological profile of DIBP resembles that of DBP. Due to its very similar application properties DIBP is one of the main marketed all-round alternatives to DBP, which the European Chemical Agency included on list of priority substances recommended to be included in Annex XIV due to reproductive toxicity.

REFERENCES

Ausschuss für Umwelthygiene (AUH, 1995): Standards zur Expositionsabschätzung. Bericht des Ausschusses für Umwelthygiene. Behörde für Arbeit, Gesundheit und Soziales, Hamburg (Hrsg.)

BASF (2003): Diisobutyl phthalate (DiBP). Prenatal developmental toxicity study in Wistar rats. Administration in the diet. Study report. Project number 32R0233/02018; cited in Saillenfait, A.M. and Laudet-Hesbert, A. (2005): Phthalates (II). EMC-Toxicologie Pathologie, 2, 137-150

BASF (1996): Vertrauliche Aktennotiz zu Produktion, Import/Export und Emissionen des Isobutylphthalates, Schriftl. Mitteilung Dr. Bias, BASF AG vom 15.11.1996; cited in BUA Report 201 (1997)

Becker, K., Conrad, A., Lusansky, C., Schulz, C., Seiwert, M., Hünken, A. and Kolossa-Gehring, M. (2008): German Environmental Survey for Children (GerES IV): Metabolites of DEHP, DnBP, DiBP , BBzP, and DiNP in urine of German children. Joint Annual Conference of ISEE/ISEA, Pasadena, California USA on October 12-16, Lecture and Abstract 1397

BfR, Bundesinstitut für Risikobewertung (2007): Di-isobutylphthalate in food-contact paper and board. Minutes of the meeting of the working group “Paper and board” on 5 July 2007 at BfR; http://www.bfr.bund.de/

Boberg, J., Metzhoff, S., Wortzinger, R., Axelstadt, M., Brokken, L., Vinggaard, A.M., Dalgaard, M, and Nellemann, C. (2008): Impact of diisobutyl phthalate and other PPAR agonists on steroidogenesis and plasma insulin and leptin levels in fetal rats. Toxicology, 250, 75-81

Bononi, M. and Tateo, F. (2009): Identification of Diisobutyl Phthalate (DIBP) suspected as possible contaminant in recycled cellulose for take-away pizza boxes. Packaging Technology and Science, 22, 53-58

Borch, J., Axelstad, M., Vinggaard, A.M. and Dalgaard, M. (2006): Diisobutyl phthalate has comparable anti-androgenic effects to di-n-butyl phthalate in foetal rat testis. Toxicol. Lett., 163, 183-190

Bopp, K. and Altkofer, W. (2009): Survey on intake of certain phthalic acid esters in South Germany – comparative study of two boarding schools with conventional and organic nutrition. Deutsche Lebensmittel-Rundschau 105 (35), 35-38

BUA Report 201 (1997): Diisobutylphthalat. ed. by the GDCh_advisory Committee on Existing Chemicals of Environmental Relevance (BUA), S. Hirzel, Wissenschaftliche Verlagsgesellschaft, Stuttgart

Butte, W., Hostrup, O. and Walker, G. (2008): Phthalate im Hausstaub und in der Luft: Assoziationen und mögliche Quellen in Wohnräumen. Gefahrstoffe - Reinhaltung der Luft 68, 3, 79-81

BVL, Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (2008a): Berichte zur Lebensmittelsicherheit 2007: Bundesweiter Überwachungsplan. Basel – Boston – Berlin, ISBN 978-3-7643-8916-1

BVL, Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (2008b): Kontaminanten in Lebensmittelverpackungen aus Papier, Karton und Pappe. (interner Bericht)

Cao, X.-L. (2008): Determination of phthalates and adipate in bottled water by headspace solid-phase microextraction and gas chromatography/mass spectrometry. J. Chromatogr., A 1178, 231-238

CSTEE, Scientific Committee on Toxicity, Ecotoxicity and the Environment (2004): Opinion on the Risk Assessment for acetyl-tributyl-citrate (ATBC) Plasticizer used in children's toys. C7GF/csteeop/ATBC/080104 D(04), adopted on 8 January 2004

Danish EPA, Danish Environmental Protection Agency (2006): Borling, P., Engelund, B., Sorensen, H. and Cohr, K.-H.: Survey, migration and health evaluation of chemical substances in toys and childcare products produced from foam plastic. Survey of Chemical Substances in Consumer Products, No. 70
http://www2.mst.dk/common/Udgivramme/Frame.asp?http://www2.mst.dk/udgiv/publications/2006/87-7052-098-4/html/helepubl_eng.htm

Danish EPA, Danish Environmental Protection Agency (2007): Svendsen, N., Bjarnov, E. and Poulsen, P.B.: Survey as well as health assessment of chemical substances in school bags, toy bags, pencil cases and erasers. Survey of Chemical Substances in Consumer Products, No. 84
http://www2.mst.dk/Udgiv/publications/2007/978-87-7052-547-3/pdf/978-87-7052-549-7.pdf

EFSA (2008): Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) on a request related to a 18th list of substances for food contact materials. EFSA Journal (2008) 628-633, 1-19

Foster, P.M.D., Lake, B.G., Thomas, L.V., Cook, M.W. and Gangolli, S.D. (1981): Studies on the testicular effects and zinc excretion produced by various isomers of monobutyl-o-phthalate in the rat. Chem.-Biol. Interactions, 34, 233-238

Fromme, H., Gruber, L., Schlummer, M., Wolz, G., Böhmer, S, Angerer, J., Mayer, R., Liebl, B. and Bolte, G. (2007): Intake of phthalates and di(2-ethylhexyl)adipate: Results of the Integrated Exposure Assessment Survey based on duplicate diet samples and biomonitoring data. Environment International, 33 (8), 1012-1020

Hardin, B.D., Schuler, R.L., Burg, J.R., Booth, G.M., Hazelden, K.P., MackKenzie, K.M., Piccirillo, V.J. and Smith, K.N. (1987): Evaluation of 60 chemicals in a preliminary developmental toxicity test. Teratogen. Carcin. Mutag., 7, 29-48

Harris, C.A., Henttu, P., Parker, M.G. and Sumpter, J.P. (1997): The oestrogenic activity of phthalate esters in vitro. Environ. Health Perspect., 105 (8), 802-811

Härtel, G.H. (1985): Low-volatility polar organic solvents for sulfur dioxide, hydrogen sulfide and carbonyl sulfide. J. Chem. Eng. Data 30, 57-61

Heitmann, K. (2003): Leitfaden zur Anwendung umweltverträglicher Stoffe: Teil 5.1: Weichmacher. Umweltbundesamt Berlin, FKZ 201 28 213

Heudorf, U. (2007): Kindergesundheit und Umwelt. Belastung von Kindern mit Acrylamid, Phthalaten und Nebenstromrauch,. Stadtgesundheitsamt Frankfurt, Frankfurt 2007
http://www.frankfurt.de/sixcms/media.php/738/Bericht%20Kind%20und%20Umwelt.pdf

Hodge, H.C. (1954): Preliminary acute toxicity tests and short term feeding tests of rats and dogs given di-isobutyl phthalate and dibutyl phthalate. Office of Toxic substances, Microfiche No. 205995 v. 28.01.1983, 179; cited in BUA Report 201 (1997)

Howdeshell, K.L., Wilson, V.S., Furr, J., Lambright, C.R., Rider, C.V., Blystone, C.R., Hotchkiss, A.K. and Gray, L.E. (2008): A mixture of five phthalate esters inhibits fetal testicular testosterone production in the Sprague-Dawley rat in a cumulative, dose-additive manner. Toxicol, Sci., 105 (1), 153-165

Hüls (1995): Stoffbericht Diisobutylphthalat, Schriftliche Mitteilung Dr. Weiß, Hüls AG, 27.06.1995; cited in BUA Report 201(1997)

KEMI (2006): Risk reduction strategy DEHP, draft of March 2006

Kinder-Umwelt-Survey (KUS), German Environmental Survey 2003/06 (GerES IV) for Children, Schlußbericht September 2008, Umweltbundesamt, Dessau-Roßlau, Berlin (not published); see:
Becker, K., Schulz, C., Babisch, W., Dürkop, J., Roskamp, E., Seiwert, M., Szewzyk, R., Ullrich , D. and Seifert B (2005) German environmental survey for children (GerES IV) 2003-2006. Pollution Atmosphérique, 188, 475-479 and
http://www.umweltbundesamt.de/gesundheit-e/survey/index.htm

Leyder, F. and Boulanger, P. (1983): Ultraviolet absorption, aqueous solubility and octanol-water partition for several phthalates. Bull. of Environm. Contam. Toxicol. 30, 152-157

Mentlein, R. and Butte, W. (1989): Hydrolysis of phthalate esters by purified rat and human carboxylesterases. Biochem. Pharmacol., 38, 3126-3128

Nederlandse Organisatie voor toegepast-natuurwetenschappelijk onderzoek (TNO): Tukker, A. (2001): Alternatives for Phthalates. TNO-rapport STB-01-55

Nederlandse Organisatie voor toegepast-natuurwetenschappelijk onderzoek (TNO): Tukker, A. (2002): Inventory of Plasticisers. TNO-rapport STB-01-56

Nishihara, T., Nishikawa, J., Kanayama, T., Dakeyama, F., Saito, K., Imagawa M., Takatori, S., Kitagawa, Y., Hori, S. and Utsumi, H. (2000): Oestrogenic activities of 517 chemicals by yeast two-hybrid assay. J. Health Sci., 46 (4), 282-298

Oishi, S. and Hiraga, K. (1980a): Effects of phthalic acid monoesters on mouse testes. Toxicology Letters, 6, 239-242

Oishi, S. and Hiraga, K. (1980b): Effect of phthalic acid esters on mouse testes. Toxicol. Lett., 5, 413-416

Oishi, S. and Hiraga, K. (1980c): Testicular atrophy induced by phthalate acid esters: Effect on testosterone and zinc concentrations. Toxicol. Appl. Pharmacol. 53, 35-41

Oishi, S. and Hiraga, K. (1980d): Testicular atrophy induced by phthalic acid monoesters: effects of zinc and testosterone concentrations. Toxicology 15,197-202

Pfordt, J. (2004): Di(2-ethylhexyl)phthalat und Dibutylphthalate in einigen Lebensmitteln mit Kunststoffverpackungen und in Frauenmilch. Deutsche Lebensmittel-Rundschau, 11, 431- 436.

Potin-Gautier, M., Grenier, P. and Bonastre, J. (1982): Nouvelle application analytique de la methode de determination des pressions de vapeur par saturation d'un gas inerte. Anal. Lett. 15, 1431-1448

Risk & Policy Analysts Limited (2000): The Availability of Substitutes for Soft PVC Containing Phthalates in Certain Toys and Childcare Articles. Final Report, Project: J317/PHTH, prepared for European Commission, Directorate-General Enterprise

Saillenfait, A.M., Sabate, J.P. and Gallissot, F. (2005): Developmental toxic effects of diisobutylphthalate administered by gavage to rats. Toxicology, 213; 231-232

Saillenfait, A.M., Sabaté, J.P. and Gallissot, F. (2006): Developmental toxic effects of diisobutylphthalate, the methyl-branched analogue of di-n-butyl phthalate. Toxicol. Lett., 165, 39-46

Saillenfait, A.M., Sabaté, J.P. and Gallissot, F. (2008): Diisobutyl phthalate impairs the androgen-dependent reproductive development of the male rat. Reprod. Toxicol., 26, 107-115

SCCP, Scientific Committee on Consumer Products (2007): Opinion on phthalates in cosmetic products. SCCP/1016/06, adopted on 21 March 2007
http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_106.pdf

Shen, H.-Y. (2005): Simultaneous screening and determination eight phthalates in plastic products for food use by sonication-assisted extraction/GC-MS methods. Talanta, 66, 734-739

Singh, A.R., Lawrence, W.H. and Autian, J. (1972): Teratogenicity of phthalate esters in rats. J. Pharm. Sci., 61 (1), 51-5

Statistisches Bundesamt (1994): Außenhandel nach Waren und Länder (Spezialhandel) – Dezember und Januar 1993, Verlag Metzler-Poeschel, Stuttgart, Nr. 29173100; cited in BUA Report 201 (1997)

Stiftung Warentest (2008a): Schadstoffe in Schulbedarf, September, 76-81

Stiftung Warentest (2008b): Kinderlaufräder, Juli, 72-76

Stuer-Lauridsen, F., Mikkelsen, S., Havelund, S., Birkved, M., Hansen, L.P. and COWI Consulting Engineers and Planners AS (2001): Environmental and Health Assessment of Alternatives to

Phthalates and to flexible PVC, Miljøstyrelsen Miljøprojekt – Miljøproject No. 590

Swan, S., Main, K., Liu, F., Stewart, S., Kruse, R., Calafat, A., Mao, C., Redmon, J., Ternand, C., Sullivan, S., Teague, J. and The-Study-for-Future-Families-Research-Team (2005): Decrease in anogenital distance among male infants with prenatal phthalate exposure. Environ. Health Perspect., 113, 1056-1061

Takeuchi, S., Iida, M., Kobayashi, S., Jin, K., Matsuda, T. and Kojima, H. (2005): Differential effects of phthalate esters on transcriptional activities via human oestrogen receptors α and ß, and androgen receptors. Toxicology, 210, 223-233

Toda, C., Okamoto, Y., Ueda, K., Hashizume, K., Itoh, K. and Kojima, N. (2004): Unequivocal oestrogen receptor-binding affinity of phthalate esters feaured with ring hydroxylation and proper alkyl chain size. Arch. Biochem. Biophys., 431, 16-21

Wittassek, M. and Angerer, J. (2008): Phthalates: metabolism and exposure. Int. J. Androl., 31 (2), 131-8

Woodward, K.N. (1988): Phthalate Esters: Toxicity and Metabolism. Boca Raton: CRC Press, 1, 49

Wormuth, M., Scheringer, M., Vollenweider, M. and Hungerbühler, K. (2006): What are the sources of exposure to eight frequently used phthalic acid esters in Europeans? Risk Analysis, 26, 803-824